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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EDWARDS & ANGELL, LLP			WILDER, CYNTHIA B	
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1637

DATE MAILED: 12/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/529,397

Applicant(s)

YOKOYAMA ET AL.

Examiner

Cynthia B. Wilder, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 October 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19-35 is/are pending in the application.
- 4a) Of the above claim(s) 31-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19-21 is/are rejected.
- 7) ☒ Claim(s) 22-30 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 April 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/9/03</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's preliminary amendment filed on 4/11/2000 and supplemental amendments filed on 5/6/2004 and 7/6/2004 are acknowledged and has been entered. Additionally, the Examiner acknowledges the typographical error found in SEQ ID NO: 63 on page 25 of the specification. A review of the Application has established that no new matter is present.

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 19-30 and SEQ ID NO: 25, in the reply filed on October 15, 2004 is acknowledged. The traversal is on the ground(s) that the Office action has not asserted any prior art document that teaches a nucleic acid capable of being specifically bound to target protein of Ras. Applicant asserts that the disclosure teaches a PCR primer for amplifying nucleic acid containing K-ras. Applicant states that moreover, Vogelstein patent does not refer to Ras proteins or a nucleic acid capable of being specifically bound to Ras. Applicant states that thus the office action has not satisfied its burden to show that Groups I-II lack a special technical feature that is the same or that corresponds to a special feature of the other claimed invention. Applicant request withdrawal of the restriction requirement and rejoinder of the claimed invention of Groups II and III. In response to the sequence election requirement, Applicant asserts that MPEP 1850 states that the USPTO has partially waived 37 C.F.R. 1.475 and 1.499 et seq. allow applicants to claim up to ten (10) nucleotide sequences in one applicant, even when they may not have the same or corresponding technical feature. APPLICANT STATES THAT ACCORDLING, Applicant request examination of SEQ Id NOS: 19-24 and SEQ ID NOS; 26-28 in addition to provisionally elected SEQ ID NO: 25 giving a total of 10 sequences comprising SEQ ID NOS: 19-28.

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The examiner acknowledges Applicant's arguments. However the arguments are not found persuasive because for the following reasons: Firstly, the courts have established that during patent examination the pending claims must be interpreted as broadly as their terms reasonably allow (*In re Zeltz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed Cir, 1989). In this case, the claims as broadly written with the open language "capable of" can be interpreted to encompass nucleic acids which may specifically bind to a Ras protein **or** nucleic acids which may not be specifically bound to a Ras protein. The claims as broadly written are not limited in the manner which Applicant implies. Thus, Vogelstein meets the limitation of the claims as discussed in the previous Office Action. Secondly, in response to Applicant's arguments concerning the sequence election requirement, It is noted that the limitation "up to ten" independent and distinct nucleotide sequences" is interpreted by the Office as being equivalent to "one" independent and distinct nucleotide sequence. In this case, the claims disclose 63 different nucleotide sequences but only require at least one of the sequences for the product of invention I. Since the different sequences are distinct one from the other, an undue search burden would be required of the examiner if all of the different 63 sequences were search. Accordingly, a restriction between the claims and sequences are still deemed proper and is therefore made FINAL. Claims 1-18 have been canceled. Claims 19-35 are pending. Claims 19-30 and SEQ ID NO: 25 have been elected and discussed in this Office action. The claims 31-35 have been withdrawn from consideration as being drawn to a non-elected invention.

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Priority

2. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in the instant application. Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on October 9, 2003 is acknowledged and has been considered by the Examiner. It is noted that Applicant has provided several non-patent literature documents filed on April 11, 2000 that have not been listed in the form-1449. For full consideration of the documents, it is suggested submitting a form-1449 which includes a list of the references submitted therein. It further noted that the documents have been reviewed by the Examiner.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to at pages 6-10, 14-17 and 24-25 because the designation for the sequence identifier is improper (see MPEP§ 2422.03). It is suggested amending the disclosure to recite --SEQ ID NO:--.

Appropriate correction is required.

Claim Objections

4. Claims 22-30 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claims should refer to other claims in the alternative only and/or cannot

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depend from any other multiple dependent claims. See MPEP § 608.01(n). Accordingly, the claims 22-30 have not been further treated on the merits.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 19-21 are rejected under 35 U.S.C. 101 because the claims are drawn to a nucleic acid, which reads on a product of nature such as e.g., a mRNA. The claim should be amended to indicate the hand of the inventor, for example, the insertion of "isolated" in connection with the nucleic acid to identify a product not found in nature (see MPEP 2105).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an RNA aptamer comprising the sequence of SEQ ID NOS: 1-28 which specifically binds to a target protein of Ras, wherein said target protein of Ras is Raf-1, does not reasonably provide enablement for a nucleic acid capable of being specifically bound to a target protein of RNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining

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whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is "undue". These factors include but are not limited to: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented in the specification, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the unpredictability of the art and (8) the breadth of the claims. (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)) (*MPEP* 2164.01(a)). The claimed invention is drawn to a nucleic acid capable of being specifically bound to a target protein of Ras. The specification at page 5 discloses that the invention is drawn to a novel nucleic acid molecular seed bound to a "target protein of Ras". At page 7 the specification discloses that examples of the "target proteins of Ras" of the present invention include Raf-1, B-Raf, RGL, Ral, GDS, MELL, P13K and the like. At page 8, the specification teaches that the nucleic acid molecular seed of the present invention comprises any one of base sequences, SEQ ID NOS: 1-28, preferably sequences of SEQ ID NO: 1 to 8 or sequences of SEQ ID NOS: 25 to 28. The examples beginning at page 20 of the specification teaches the purification of a glutathione S-transferase and a fusion protein of the Ras binding domain of Raf-1, in vitro selection of RNA, selection of RNA bound to Raf-1 (Ras binding domain), cloning and determination of a sequence, measurement of a kD value and binding inhibition of Ras based on the RNA sequence being specifically bound to Raf-1. No enabling disclosure is found in the specification for the invention as broadly claimed. The specification does not adequately describe or disclose any of the numerous nucleic acid sequences, including variant sequences, mutations and polymorphisms which may or may not be bound to a target protein of Ras.

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Likewise, there is no enabling disclosure which describes or disclose wherein any nucleic acid is capable of being bound to any of the different target protein of Ras know in the art, such as B-Raf, RGL, Ral, GDS, MELL, P13K and the like, besides Raf-1. The specification provides no guidance teaching the skill artisan how to make or use the invention commensurate fully in scope. Therefore undue experimentation would be required of the skill artisan to determine every nucleic acid molecule capable of binding to any and all of the target proteins of Ras.

Furthermore, Applicant has provided no guidance beyond the mere presentation of nucleic acid sequences SEQ ID NOS: 1-28 which may specifically bind to the target protein of Ras, Raf-1. There is however, no evidence that these sequences as disclosed in SEQ ID NOS: 1-28 are capable of binding to any of the other target proteins of Ras, such as B-Raf, RGL, Ral, GDS, MELL, P13K and the like. There is no guidance or enabling disclosure which suggest that any mutation, variant, polymorphism, or etc of a nucleic acid sequence as encompassed by the claims or the sequences of SEQ ID NOS: 1-28 would result in a nucleic acid molecule being capable of specifically binding to a target protein of Ras, including Raf-1. Thus, the full scope of the claimed invention is not reproducible due to the lack of guidance and absence of working examples in the specification. Likewise, a large quantity of experimentation would be required by the skilled artisan to determine which nucleic acids sequences effectively and specifically binds to each and every target protein of Ras and as such what effect these interaction have on the target protein and Ras. To reiterate, the specification does not provide an isolated nucleic acid molecule that bears a reasonable correlation to the entire scope of the claims. As to the level of predictability and unpredictability in the art, the level of skill in the art at the time of the invention is very high. However, the level of unpredictability in molecular biology is also high.

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In fact the art teaches that the molecular mechanism of the cellular signaling involving Ras and its target proteins is complicated, thus making it important to elucidate the role of each protein-protein interaction (Kimoto et al, Febbs Letter (1998), 322-326). The art also teaches that other means of specific recognition for Raf-1 may also have been conceivable including the development of RNA aptamers to the raf-1 protein. However, such techniques are time consuming and expensive making them inappropriate for a clinical test (US 6521,407, col. 13, lines 18-22). Thus, giving the unpredictability in the art, the lack of guidance and absence of working examples in the specification, the complex nature of the invention and the breadth of the claims which fails to recite more specifically which isolated nucleic acids specifically binds to which target protein of Ras, undue experimentation is required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112: Written Description

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claimed invention is drawn to a nucleic acid capable of being specifically bound to a target protein of Ras, wherein said nucleic acid is RNA. The specification teaches at pages

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1 and 7 that the "target proteins of Ras" include Raf-1, B-Raf, RGL, Ral, GDS, Mekk, P13K and the like. However, in the Examples and Best Mode of Carrying out the Invention, Applicant only discloses the RNA aptamers disclosed in SEQ ID NOS: 1-28 being specifically bound to the Raf-1, which is one of the target proteins of Ras. The claims as written encompass numerous nucleic acids species, including products of nature and target protein of Ras that have not been adequately described or disclosed in the specification as filed. Likewise, the claims as written encompass any numerous variant sequences, mutations, polymorphisms, deletion, substitutions and frameshift mutations and etc, which are not adequately described or disclosed anywhere in the specification as filed. There is no disclosure found in the specification that adequately supports the claims commensurate fully in scope. A representative number of nucleic acid species for each genus must be disclosed to meet the written description requirement of 112, first paragraph. As set forth by the Court in *Vas Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date Applicant was in possession of the claimed invention. Absent a written description disclosing a representative number of the species as claimed in claims 19-21 of the specification fails to show that Applicant was, in fact "in possession of the claimed invention" at the time the application for patent was filed.

Claim Rejections - 35 USC § 102(b)

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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9. Claims 19 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Avruch et al (5582995, December 10, 1996). Regarding claims 19 and 21, Avruch et al teach an isolated nucleic acid molecule capable of binding to a target protein of Ras, wherein said nucleic acid is specifically bound to the Ras binding domain of a target protein of Ras (col. 6, lines 5-13). Therefore, Avruch et al meets the limitations of claims 19 and 21 of the instant invention.

10. Claim 19 is rejected under 35 U.S.C. 102(b) as being by anticipated by Freed et al (US 5597719, January 28 1997). Regarding claim 19, Feed et al teach an isolated nucleic acid compound capable of binding to a target protein of Ras (col. 7, lines 24-44). Therefore, Freed et al meets the limitations of the claims of the instant invention.

Claim Rejections - 35 USC § 102(a)

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 19-21 are rejected under 35 U.S.C. 102(a) as being anticipated by Kimoto et al (FEBS Letter, Vol. 441, pages 322-326, December 18. 1998). Regarding claims 19-21, Kimoto et al teach an isolated nucleic acid capable of being specifically bound to a target protein of ras, wherein said nucleic acid is RNA and wherein said nucleic acid is specifically bound to the ras binding domain of the target protein of Ras (Abstract and section 3.1 and Figures 2 and 4). Therefore, Kimoto et al meets the limitations of the instant invention.

13. Claim 19 is rejected under 35 U.S.C. 102(a) as being anticipated by Vogelstein et al (US 5910407, June 1999). Regarding claim 19, Vogelstein et al teach an isolated nucleic acid capable of binding to a target protein of ras (col. 5, lines 2-22). Therefore, Vogelstein et al meets the limitation of claim 19¹.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(c) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

15. Claims 19-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Sherman et al (US 2003/0170751, September 11, 2003). Regarding claims 19-21, Sherman et al teach a isolated nucleic acid capable of binding to a target protein of Ras, wherein said nucleic acid is RNA or DNA and wherein said nucleic acid is specifically bound to the Ras binding domain of

¹ It is noted that the claims have been given their broadest, reasonable interpretation. The broad language "capable of" encompasses sequence that may or *may not* bind specifically to a target protein of ras.

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the target protein of Ras (paragraphs 0043 to 0045 and 0071). Therefore, Sherman et al meets the limitations of claims 19-21 of the instant invention.

Conclusion

16. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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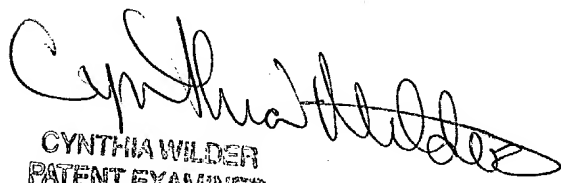
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CYNTHIA WILDER
PATENT EXAMINER
12/22/04